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(54) APPAREIL ET METHODE POUR LA DETECTION ET LE DIAGNOSTIC DE LA MALADIE PAR LA MESURE DE L'IMPEDANCE ELECTRIQUE DANS LE CORPS

(54) ELECTRICAL IMPEDANCE METHOD AND APPARATUS FOR DETECTING AND DIAGNOSING DISEASES

(57)

A method and apparatus for screening, sensing, or diagnosing disease states by obtaining a plurality of electrical impedance data measurements in organized patterns from two anatomically homologous body regions, one of which may be affected by disease. One subset of the data so obtained is processed, compared and analyzed by structuring the data values as elements of n x n impedance matrix, and characterizing these matrices by their eigenvalues and eigenvectors. Another, not entirely exclusive subset of the data is alternatively processed, compared and analyzed by plotting the impedance data as chords of two circles representing the two homologous body regions. Impedance chord plots provide a visual indication of certain disease states and their location.

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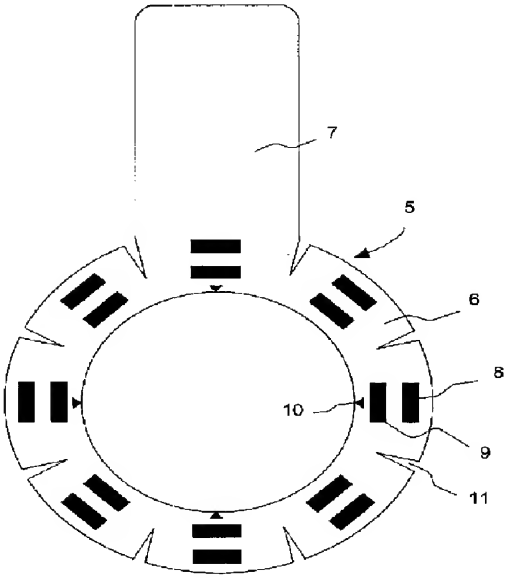
(54) **ELECTRICAL IMPEDANCE METHOD AND APPARATUS FOR DETECTING AND DIAGNOSING DISEASES**



(57) A method and apparatus for screening, sensing, or diagnosing disease states by obtaining a plurality of electrical impedance data measurements in organized patterns from two anatomically homologous body regions, one of which may be affected by disease. One subset of the data so obtained is processed, compared and analyzed by structuring the data values as elements of n x n impedance matrix, and characterizing these matrices by their eigenvalues and eigenvectors. Another, not entirely exclusive subset of the data is alternatively processed, compared and analyzed by plotting the impedance data as chords of two circles representing the two homologous body regions. Impedance chord plots provide a visual indication of certain disease states and their location.

ELECTRICAL IMPEDANCE METHOD AND APPARATUS FOR DETECTING AND DIAGNOSING DISEASES

Inventor: **Leslie W. Organ,** Charleston, SC

Date: **April 25, 1998**

ABSTRACT

A method and apparatus for screening, sensing, or diagnosing disease states by obtaining a plurality of electrical impedance data measurements in organized patterns from two anatomically homologous body regions, one of which may be affected by disease. One subset of the data so obtained is processed, compared and analyzed by structuring the data values as elements of $n \times n$ impedance matrix, and characterizing these matrices by their eigenvalues and eigenvectors. Another, not entirely exclusive subset of the data is alternatively processed, compared and analyzed by plotting the impedance data as chords of two circles representing the two homologous body regions. Impedance chord plots provide a visual indication of certain disease states and their location.

CONTENTS

FIELD OF THE INVENTION

The present invention relates to a method and apparatus for detecting or diagnosing disease states in a living organism by using a plurality of electrical impedance measurements.

BACKGROUND OF THE INVENTION

Methods for screening and diagnosing diseased states within the body are based on sensing a physical characteristic or physiological attribute of body tissue, then distinguishing normal from abnormal states from changes in the characteristic or attribute. For example, X-ray techniques measure tissue physical density, ultrasound measures acoustic density, and thermal sensing techniques measures differences in tissue heat. Another measurable property of tissue is its electrical impedance; i.e., the resistance tissue offers to the flow of electrical current through it. Values of electrical impedance of various body tissues are well known through studies on intact humans or from excised tissue made available following therapeutic surgical procedures. In addition, it is well documented that a decrease in electrical impedance occurs in tissue as it undergoes cancerous changes. This finding is consistent over many animal species and tissue types, as summarized by Pethig and Kell[1]. Human breast cancers, in particular, have shown similar changes in studies such as those of Chaudhary et al.[2] and Surowiec et al.[3] Both groups examined surgically excised normal and malignant human breast tissue and obtained similar results; i.e., on average, the electrical impedance of breast cancer tissue was about one-third that of the normal surrounding breast tissue.

Electrical impedance imaging has been proposed to create a picture of electrical impedance differences within a body region[4,5,6] much as an X-ray provides a picture of differences in physical density. One of the incentives to do so is the potential application of electrical impedance imaging as a screening technique for breast cancer, either as a replacement of or supplement to X-ray mammography. Mammography has reasonable sensitivity for detecting abnormalities when present, but the technique fails to detect about 5 to 15% of breast cancers. This is due to several factors, including concealment of the cancer by overlying normal, but dense, breast tissue, failure of mammography to image certain portions of the breast, as well as errors in perception. Mammography has relatively low success for distinguishing malignancies from other abnormalities, and of the approximately 500,000 breast biopsies performed in the United States each year because of an abnormality detected on mammography, only 15 to 30% of the biopsies reveal cancer. This lack of specificity not only results in needless anxiety and an unnecessary procedure, but adds a significant cost to the breast cancer screening program.

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There have been a number of reports of attempts to detect breast tumors using electrical impedance imaging.[4,5,6,7,8,9,10] However, there are basic problems when trying to construct an image from impedance data. The paths through tissue of X-rays are straight lines. In contrast, electrical current does not proceed in straight lines or in a single plane; it follows the path of least resistance, which is inevitably irregular and 3 dimensional. As a result, the mathematics for constructing the impedance image is very complex and requires simplifying assumptions that greatly decrease image fidelity and resolution. Not surprisingly, in view of the image reconstruction difficulties, either no clinical data were published in any of these reports, or if they were, the images were of low resolution and difficult to interpret.

SUMMARY OF THE INVENTION

The present invention scans for the presence or absence of breast abnormalities, particularly benign and malignant tumors. While not intending to be bound by any particular theory, the method of the invention may arise from the following assumptions and hypotheses:

1. The tumor will occur in only one breast.
2. Both breasts are structurally similar, and therefore can be expected to be approximate mirror images with respect to their impedance characteristics.
3. If impedance measurements are taken in a multiplicity of directions or paths across the breast (I call this an impedance scan), the presence of tumors, which are known to have a significantly lower impedance than the normal tissue they replace, will distort or change the impedance in at least some of the paths of current flow.
4. The magnitude of decreased impedance is greater for malignant tumors than for benign ones, providing a method for differentiating between these tumor types.
5. There will always be some differences in impedance between breasts in the normal individual; but these differences will be less than the differences when a cancer is present. In additional, cancer differences may have unique characteristics. This concept of "difference between differences" (impedance difference between breasts without a cancer *versus* impedance difference between breasts with a cancer) is one of the novel methods used for data analysis.

Impedance data from scanning both breasts are compared and differences are displayed and analyzed. The use of impedance differences "subtracts out" an otherwise complex and voluminous amount of impedance data produced by most current paths that, while irregular and 3 dimensional, are nevertheless substantially impedance-identical because the paths were virtually identical in both breasts. The differences that remain are much more manageable analytically, and can be used to identify abnormalities.

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An important aspect of the invention is the electrode array, designed and fabricated so that electrode position and spacing are, as closely as possible, identical in the two breasts in order not to introduce artifactual differences related to the array itself. Another aspect of the invention that contributes to the simplicity and reliability of the impedance scanning method, is the design and implementation of the apparatus for acquiring, displaying, and analyzing the data.

Whereas a primary objective of the present invention is to provide a novel and improved method and apparatus for detecting and locating breast cancers, the invention can also be applied to other diseases or conditions in which there is a distinguishable difference in electrical impedance in the tissue as a result of the disease or condition. For example, the occurrence of a deep venous thrombosis in the thigh or leg would cause a change in the circulatory dynamics which would be reflected by a change in the electrical impedance of the affected region.

A further objective of the present invention is to provide a novel and improved method and apparatus for detecting and locating diseases or conditions in any region of the body in which the electrical impedance of the region containing the disease or condition can be compared to an essentially identical, normal body region; for example, right and left forearms, right and left thighs, or right and left calves.

A still further objective of the present invention is to provide a novel and improved method and apparatus for detecting and locating diseases or conditions in any region of the body in which the electrical impedance of the region containing the disease or condition can be compared to another normal body region that, while not entirely identical, is consistently and constantly different; for example, right and left sides of the abdomen.

DESCRIPTION OF THE DRAWINGS

FIG. 1 is an illustration of the four electrode impedance measurement technique;

FIG. 2 is an illustration of the breast electrode array of the invention;

FIG. 3A is an illustration of a positioning template for the breast electrode array;

FIG. 3B is an illustration of a positioning ring for the breast electrode array;

FIG. 4 shows an implementation of lead wiring for the breast electrode array;

FIG. 5 is a block diagram of the apparatus of the invention;

FIG. 6 is a plot of an impedance matrix, a method of the present invention, obtained from a subject with cancer in the left breast;

FIG. 7 is a bar plot of the 28 Z_{same} subset of impedances, obtained from a subject with cancer in the right breast;

FIG. 8 illustrates the four possible chord lengths of a circle when there are eight equally spaced points on its circumference;

FIG. 9 is a chord plot of the 28 Z_{same} subset of impedances for the same subject used for FIG. 7. The breasts are symbolized as circles and the 28 impedances have been normalized, their anatomic direction represented by chords of a circle, and their magnitude represented by the density of shading;

FIG. 10 is a further refinement of FIG. 9 in which mirror image matching impedance chords have been removed; and

FIG. 11 is a diagnostic algorithm used for breast cancer screening based on impedance scanning.

DETAILED DESCRIPTION OF THE INVENTION

Electrical Impedance and the Four Electrode Measurement Technique.

Electrical impedance is most accurately measured by using four electrodes as shown in FIG. 1. The outer pair of electrodes **1** is used for the application of current *I*, and the inner pair of electrodes **2** is used to measure the voltage *V* that is produced across the tissue (or generally, material) **3** by the current. The current *I* flowing between electrodes **1** is indicated by the arrows **4**. The impedance *Z* is the ratio of *V* to *I*; i.e., $Z = V/I$. It is well known that using separate electrode pairs for current injection and voltage measurement produces a more accurate measurement of impedance because polarization effects at the voltage measurement electrodes are minimized.

Impedance consists of two components, resistance and capacitive reactance (or equivalently, the magnitude of impedance and its phase angle). Both components are measured, displayed, and analyzed in the present invention. However, for the purpose of explanation of the invention, only resistance will be used and will interchangeably be referred to as either resistance or the more general term impedance.

The Breast Electrode Array

FIG. 2 discloses a breast electrode array **5** of the invention that has eight electrode pairs, each pair consisting of an outer electrode **8** for current injection and an inner electrode **9** for voltage measurement. The illustrated implementation of the array has a main section **6** and a tail section **7**. Eight pairs of rectangular electrodes in circular orientation are shown, but there are many alternatives that could be advantageously used with the present invention: more electrode pairs; different electrode shapes; other shapes for the main body and tail sections of the array; and other geometrical arrangements of the electrodes, e.g., radial sectors with three or more electrodes. Regardless of the electrode arrangement, four electrodes must be used for each impedance measurement, two outer electrodes between which current is injected, and two inner electrodes at which voltage is measured. The electrodes are attached to the skin side of the main section **6** of the array **5** and are made of an electrically conductive, self-adhesive material so that when the array is positioned on the skin and pressed against it, the adhesive quality of the electrodes assures good skin fixation. Alternatively, additional adhesive material can be used at various positions on the main section **6** and/or the tail section **7** of the array. In order to assure impedance is measured in all regions of the breast, electrode arrays **5** are made in different sizes for use in women with different breast cup sizes.

For clarity of description, lead connections for the electrodes are not shown in FIG. 2. The material used for the main section **6** of the array **5**, and to a lesser degree for tail section **7**, may be flexible to allow the array to conform to the shape of the breast. Shape conformity is further aided by cutouts or darts **11** that allow the material to overlap and thereby prevent it from crumpling and possibly lifting part or all of an electrode off the skin. More accurate and consistently identical positioning of electrode arrays on both breasts is aided by the index marks **10** shown at four locations on the inner edge of the main section **6**. Before applying an array to the skin surface of the breast, a transparent, flexible positioning template **12**, shown in FIG. 3A., is positioned on the breast with central cutout **15** centered about the nipple and the template rotated so that crosshair line **16** is aligned with the body's vertical axis and crosshair **17** is aligned with the body's transverse (horizontal) axis. An ink or other mark is made on the skin surface through the cutouts **14** of the positioning template **12.** The template is then removed and the electrode array is applied with its index marks **10** shown in FIG. 2 aligned with the ink marks on the skin. An alternative embodiment of a device for

positioning the breast electrode array, an array positioning ring **18**, is shown in FIG. 3B. It consists of a ring **19** that has an outer diameter equal to the distance between the tips of diametrically opposed index marks **10** of FIG. 2. The ring **19** of FIG. 3B has four notches **20** corresponding to each of the index marks **10** of FIG. 2. Fine crosshairs **21** extend from the inner side of ring **19** between diametrically opposed notches, with the central junction of the crosshairs serving to center the array positioning ring **18** over the nipple.

FIG. 4 shows an implementation of electrode lead wiring for the breast electrode array. Electrically conductive material is deposited or otherwise applied to both surfaces of the main section **6** (the darts **11** are not shown in this drawing) and the tail section **7** of the array as follows: On the skin side of main section **6** the conductive material has the form of "U" shaped electrode connection areas **22** and **23** for outer and inner ring electrodes respectively which are attached in position over these connection areas. Many other shapes could be used for the connection areas, the primary consideration being a large enough area to ensure low resistance electrical continuity with the skin elctrodes. Fine, conductive pathways (or leads) **24** and **25** are applied to the non-skin side of main section **6** and tail section **7**. The flexible material from which the main and tail sections are fabricated is non-conductive, and so insulates conductive pathways **24** and **25** from electrode connection areas **22** and **23**. At one end each lead **24** and **25** penetrates through main section **6** and is soldered to (or otherwise electrially attached to) the electrode connection areas **22** and **23** respectively. At their other end the leads bunch in the tail section **7** to make individual electrical contact with conductive fingers **26** to form a ribbon type connector **27**.

Alternative embodiments of electrode arrays are possible that would not necessitate the attachment of adhesive electrodes to the subject's skin. For example, the subject could lay prone on a table with an opening for the breasts to fall freely downward. A flat plate, or cone, or other shaped holder with an array of electrodes on its upper surface, could then be moved upward, guided by landmarks on the breast and/or chest wall, to compress the breast to the extent required for good electrode contact. Further compression may serve beneficially to bring a tumor closer to the electrodes, or create a breast shape more conducive to analysis. A variant of this method would position the subject between 0 and 90°, say at 45° to the horizontal, again allowing the breasts to fall through an opening with, in this embodiment, a shelf at a suitable angle, say 45°, to guide the breasts. Another variant of this method would have the subject erect, as in conventional X-ray mammography, and use, for example, mediolateral oblique and craniocaudal compression, as in conventional X-ray mammography procedure, but with electrode arrays in the compression plates.

Acquiring Impedance Data

FIG. 5 discloses a basic block diagram of the data acquisition and analysis apparatus **29** for automatically obtaining, processing and analyzing impedance measurements. For the purposes of illustration, the apparatus **29** will be described as employed for screening, locating and diagnosing breast cancer. However, it should be recognized that the method and apparatus of the invention can be employed in a similar manner for screening or diagnosis at other body sites and for other conditions and diseases. A breast electrode array **5** of 16 electrodes arranged as two concentric circles of eight electrodes each is show in FIG. 5. Conventional ECG monitoring electrodes, cut down to appropriate size with the metal tab connector intact, were used. A plurality of leads **28** is intended, in this illustration, to number 16, one for each electrode. More generally, more electrodes, other electrode arrangements, and other electrode types, could be used in this application to produce more detailed and useful results. Also, the device and method of this invention contemplate the use of a variety of electrode arrays and leads, depending on other applications for which the apparatus **29** is used.

In preparation for the acquisition of impedance data, the subject lies supine on an examining table and the skin in the area the array will be placed on is gently cleansed with alcohol to debride the surface. The breast electrode array **5** is carefully oriented with respect to body axes and centered about the nipple as previously described, and then lightly pressed against the skin over each electrode to fix the array to the skin. The breast electrode array **5** as described for the present invention may not be reusable, in which case another array would be used for the second breast. It may, however, possible to modify the design of the array to allow more than one use.

As previously described, the four electrode technique is used to measure electrical impedance. Continuous 50 kilohertz sine wave current is injected between two of the eight electrodes in the outer ring of the breast electrode array **5**. Use of this frequency and waveform is standard practice for many bioimpedance applications, but there is an extended range of useable frequencies and, to a lesser degree, other waveforms. For the right breast, the electrode pairs are numbered clockwise *1* to *8*, and for the left breast, electrode pair numbering is counterclockwise so that mirror-imaged electrode pairs will always be compared. The injected current, whose amplitude is low enough that it is imperceptible, creates electric field potentials (voltages) throughout the entire breast and adjacent chest wall. In particular, it creates voltages at the eight electrodes in the inner ring of the electrode array. Measuring the voltage difference between any two of the inner electrodes, and dividing it by the value of the current injected between the two outer electrodes gives, by Ohm's law, the value of the impedance. For example, if current $I_{1,3}$ is defined as being applied between the outer electrodes of electrode pairs *1* and *3*, and voltage $V_{1,7}$ is measured between the inner electrodes of electrode pairs *1* and *7*, the resultant impedance Z is

$$Z = \frac{V_{1,7}}{I_{1,3}}$$

The apparatus **29** is multichannel device that is connected to electrode leads **28** from the breast electrode array **5**. A central control unit, consisting of central processing unit (CPU) **32** and RAM and ROM memories **33** and **34**, selects in rapid succession, one set of four electrodes at a time, a multiplicity of sets of two outer electrodes for current injection and two inner electrodes for voltage measurement to perform what I call an impedance scan. Four electrode impedance measurement is made by the conventionally designed impedance section **30**. The analog-to-digital (A/D) converter **31** is of known type, and converts the analog impedance measurement to a digitized form. Depending on the number of array electrodes, more than one A/D converter may be needed. Digital input data from the A/D converter **31** are processed by the CPU, where they undergoing real time analyses for error checking, routing to the monitor **35** for display of raw or processed data, as well as storage in memory for further analysis and output to the monitor **35** and printer **36**.

The total number of possible combinations of two current electrodes and two voltage electrodes is very large. However, mathematical and electrical circuit theory can show that there are only 49 such combinations that are independent and that all other combinations can be calculated from the set of 49. This set is obtained as follows: Current is applied between the outer electrodes of electrode pairs *1* and *2* and then, in turn, the voltage between the inner electrode of electrode pair *1* and all other inner electrodes are measured, i.e., $V_{1,2}$, $V_{1,3}$ ... $V_{1,8}$. Dividing each of these voltages by $I_{1,2}$, the current between outer the electrodes of electrode pairs *1* and *2*, gives the first seven impedance values. Current is next applied between the outer electrodes of electrode pairs 1 and 3, $I_{1,3}$, which will create a new pattern of electric field potentials. Then, the voltage is again measured between the inner electrode of electrode pair *1* and all other inner electrodes ($V_{1,2}$, $V_{1,3}$ ... $V_{1,8}$). Dividing each of the voltages by $I_{1,3}$ gives the next seven impedance values. This process is repeated for current

applied between the outer electrodes of electrode pairs *1* and *4*, *1* and *5*, *1* and *6*, *1* and *7*, and *1* and *8*, to produce, finally, seven sets of seven impedance values. Placing these impedance values (elements) in a *7*-row by *7*-column grid results in what I call the impedance matrix.

There is a special subset of *7* impedance values in the 49 element set – those that use the same pair of electrodes for current injection and voltage measurement; for example, current $I_{1,3}$ applied between the outer electrodes of electrode pairs *1* and *3*, and voltage $V_{1,3}$ measured between inner electrodes of the same electrode pairs gives impedance

$$Z = \frac{V_{1,3}}{I_{1,3}}$$

I call impedances in this subset Z_{same} type impedances. They are:

$$Z_{1,2} \quad Z_{1,3} \quad Z_{1,4} \quad Z_{1,5} \quad Z_{1,6} \quad Z_{1,7}$$

There is additional value, as will be disclosed under Data Analysis, in measuring all possible Z_{same} impedances, another 21 measurements, as listed below:

$$\begin{array}{cccccc} Z_{2,3} & Z_{2,4} & Z_{2,5} & Z_{2,6} & Z_{2,7} & Z_{2,8} \\ & Z_{3,4} & Z_{3,5} & Z_{3,6} & Z_{3,7} & Z_{3,8} \\ & & Z_{4,5} & Z_{4,6} & Z_{4,7} & Z_{4,8} \\ & & & Z_{5,6} & Z_{5,7} & Z_{5,8} \\ & & & & Z_{6,7} & Z_{6,8} \\ & & & & & Z_{7,8} \end{array}$$

Therefore, a complete set of impedance measurements for one breast, when the illustrated eight pair electrode array is used, consists of 49 measurements for the impedance matrix, and another 21 measurements to obtain all values for Z_{same}, resulting in a total of 70 impedance measurements for each breast. I call the organized process of selecting lead sets and obtaining these measurements an impedance scan. As the values are being acquired, their accuracy and reliability are checked in real time by a novel error detection program in the central control unit that uses algorithms based on 1) expected values of impedances related to their position in the matrix, 2) expected ratios of the resistive and reactive components of impedance, and 3) a comparison of the 21 measured Z_{same} values listed above to their calculated values derived from the impedance matrix.

Data Analysis

In the method of this invention, the breast is considered as a non homogeneous, electrically conducting object with M + 1 electrode pairs (to be referred to in this discussion simply as an "electrode," one that can be used for both current injection and voltage measurement without electrode polarization). I assign one electrode as the reference electrode with zero potential. The current at the reference electrode is the sum of the currents that are applied to the other M electrodes. The impedance matrix **Z** relates the currents I_i, the current through the *ith* electrode, and the voltages V_i, the potential difference between the *ith* electrode and the reference electrode, where i = 1,2,3,...,M, as follows:

$$\begin{bmatrix} V_1 \\ V_2 \\ V_3 \\ . \\ . \\ V_M \end{bmatrix} = \mathbf{Z} \times \begin{bmatrix} I_1 \\ I_2 \\ I_3 \\ . \\ . \\ I_M \end{bmatrix}$$

which can be condensed as $\mathbf{V} = \mathbf{Z} \times \mathbf{I}$.

For an object with M + 1 electrodes as described above, the impedance matrix **Z** is defined as an M × M matrix:

$$\mathbf{Z} = \begin{bmatrix} Z_{11} & Z_{12} & Z_{13} & . & . & Z_{1M} \\ Z_{21} & Z_{22} & Z_{23} & . & . & Z_{2M} \\ Z_{31} & Z_{32} & Z_{33} & . & . & Z_{3M} \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ Z_{M1} & Z_{M2} & Z_{M3} & . & . & Z_{MM} \end{bmatrix}$$

Each matrix element Z_{ij} (i,j = 1,2,3,...,M) is equal to V_i/I_j when all currents except the current at the *jth* electrode are equal to zero. In a given subject, the impedance matrix **Z** is unique for a given pattern of breast electrodes and therefore represents the "signature" of the breast. Once available, the **Z** matrix (or **R** matrix, or **Xc** matrix, if **Z** is resolved into its resistive and capacitive reactive components) can be used in the following ways in the present invention to screen for or diagnose disease:

1. Perform pattern recognition analyses on the matrix;
2. Examine the determinant, eigenvalues and eigenvectors of the matrix; and
3. Compute the joule losses for each breast by evaluating $P = \mathbf{I}^T \times \mathbf{Z} \times \mathbf{I}^*$ where T denotes matrix transposition and * denotes complex conjugation. If P is significantly lower for one breast, it may indicate that a cancer is present in the breast with the lower P.

The method of the present invention recognizes that an impedance matrix is not an image of the structure of the underlying breast, and indeed the complexity and impracticality of attempting to construct impedance images is purposely avoided. Instead, a relatively simple new test procedure called an impedance scan is performed in an organized fashion with inventive devices to ensure accuracy and reproducibility of results in general and precise mirroring of the procedure between two sides or two regions in particular. Impedance values are obtained in a manner that allows them to be organized into an impedance matrix. These values, the elements of the matrix, depend on the electrical characteristics of the underlying structures. Any electrical change or abnormality in a structure will produce a change in the impedance matrix. And if there is a (reasonably) identical normal structure or region, detection and diagnosis of the difference produced by the abnormality is greatly simplified by comparison with the normal structure and by clinical experience that has previously related the difference with the disease state that produced it.

A pilot study to examine the performance of the described invention was performed on two groups of subjects. The first group (biopsy group) consisted of100 subjects scheduled for breast biopsy because of a suspicious area in one breast revealed by X-ray mammogram. Immediately before the biopsy, impedance scanning was performed on both breasts. The pathology report on the biopsy material was obtained later. The second group of 20 subjects (control group) were randomly selected from those undergoing routine yearly screening mammograms. All were confirmed to have no abnormalities. An example of a graphical plot of an impedance matrix (specifically, the resistive component) in a subject found to have an infiltrating ductal adenocarcinoma in her left breast is shown in FIG. 6. The x-axis indicates the selection of outer electrodes for current injection; e.g., between electrodes *1* and *2*, between *1* and *3*, ... between *1* and *8*. As described previously, for each such selection, seven values of impedance are obtained by measuring voltages between electrodes *1* and *2*, *1* and *3*, ... *1* and *8*. In the graph, these seven impedance values are shown in order proceeding from left to right for each current selection, with impedance (resistance) magnitude indicated by the y-axis height. As predicted by the known decrease in impedance of malignant tissue, the matrix plot for the breast with a cancer has lower impedances. This effect is seen throughout in this example; in other subjects, it occurred in most, but not all regions.

Associated with certain types of matrices, including the impedance matrices as structured in the present invention, are values called eigenvalues and vectors called eigenvectors. These words are Anglo-German hybrids which use the German "eigen" for characteristic or particular. Characteristic or particular in the sense that by mathematical analysis each *7* x *7* impedance matrix can be represented by a set of seven numbers, i.e., seven eigenvalues, that are unique to that matrix. Furthermore, associated with each of these numbers (eigenvalues) is a unique, 7D vector, its eigenvector. Since the eigenvalues and eigenvectors characterize the matrix, and the matrix in turn is sensitive to tissue changes resulting from disease, an object of the present invention is the use of eigenvalues and eigenvectors as a means of detecting and diagnosing disease states. The number of eigenvalues and eigenvectors available for this purpose will vary with the size of the impedance matrix, increasing as the number of electrodes used in the array becomes larger.

Another object of the method of the present invention is to use the special set of impedance values, referred to previously as Z_{same}, as a means of detecting and diagnosing disease states. This set, for a 7 x 7 matrix, has 28 values and is shown below. Larger matrices will have correspondingly larger sets. The 28 Z_{same} values from both breasts can be plotted and compared; for example, in the bar plot

$Z_{1,2}$	$Z_{1,3}$	$Z_{1,4}$	$Z_{1,5}$	$Z_{1,6}$	$Z_{1,7}$	$Z_{1,8}$
	$Z_{2,3}$	$Z_{2,4}$	$Z_{2,5}$	$Z_{2,6}$	$Z_{2,7}$	$Z_{2,8}$
		$Z_{3,4}$	$Z_{3,5}$	$Z_{3,6}$	$Z_{3,7}$	$Z_{3,8}$
			$Z_{4,5}$	$Z_{4,6}$	$Z_{4,7}$	$Z_{4,8}$
				$Z_{5,6}$	$Z_{5,7}$	$Z_{5,8}$
					$Z_{6,7}$	$Z_{6,8}$
						$Z_{7,8}$

of FIG.*7*, obtained in the pilot study from another subject found to have early cancer of the right breast (intraductal carcinoma). Most of the bars in the breast with the cancer are lower in amplitude (smaller impedance) than corresponding bars on the normal side.

Yet another method of the present invention for the display and analysis of Z_{same} data is as follows: First, all impedance values are normalized to cancel out the effect on impedance of differences in electrode separation. For example (viewing breast array **5** in FIG. 5), even if the tissue

impedance is constant throughout, the impedance reading between electrodes *1* and *5* will be larger than the value between electrodes *1* and *2* because of the greater spatial separation between the former. As shown in FIG. 8, for an eight pair, circular electrode array there are four separation distances or chords: a 22.5° chord **37**, a 45° chord **38**, a 67.5° chord **39**, and a 90° chord **40**. The effect of electrode separation on impedance can be cancelled out and an estimate of normalized or specific impedance obtained (impedance per unit length) by setting the distance between adjacent electrodes at 1 and retaining the measured value of impedance between adjacent electrode pairs (22.5° chords), but dividing the impedance measured between 45° chords, 67.5° chords, and a 90° chords by 1.85, 2.41 and 2.61 respectively. The divisors were obtained from basic trigonometric calculations. Next, the minimum and maximum values of the 56 normalized impedance values (28 per side) for a given subject are used to define the impedance range for that subject, and the range is then subdivided into eight equal smaller size ranges, or bins. Using as an example the same subject from FIG. 7 (right breast cancer), it can be seen in FIG. 9 that the range of normalized impedances varied from 85 to 292 ohms, giving eight bins of 85 to 110, 111 to 136, 137 to 162, ... and 267 to 292 ohms. The right and left breasts are symbolized in FIG. 9 by circles, and the impedances between electrode pairs are represented as wide lines or chords. The magnitude of each impedance is indicated by the density of grey shading (or alternatively by color) with the the lowest impedances (those within the 85 to 110 ohm bin) assigned black, impedances at the next level (the 111 to 136 ohm bin) are assigned dark grey, and so on until the highest impedances (the 267 to 292 ohm bin) which are assigned white. I call FIG. 9 a chord plot of normalized impedances.

By calculating normalized impedance to more closely represent impedance per length, displaying the results as shaded chords across a circle, as in FIG.9, then removing all mirror image matching impedance chords, leaving only differences between the two sides, as shown in FIG. 10, further extends the usefulness of the method. It is now apparent that not only are the lower impedances in the right breast, but they are clustered at the inner aspect of the breast. This finding was confirmed by the X-ray mammogram for this subject – the cancer was in the mid inner right breast. I call FIG. 10 a match-removed chord plot of normalized impedances.

Another, yet further extension of the disclosed method becomes necessary on observation of difference Z_{same} impedance scans as displayed in FIG. 10 but for normal subjects. They, too, have some differences because there are always small anatomic or physiologic side-to-side differences in homologous body structures. This required the establishment of a database in which side-to-side impedance differences were examined when both breasts were normal (control group) and when one of the breasts had a cancer (cancer group). This was done in order to provide a set of statistics to distguish between impedance scans from normal subjects and those in which there was an underlying disease condition. The statistics are:

1. Mean of Algebraic Differences: The algebraic side-to-side difference beween each of the 28 Z_{same} impedance values is taken, and the mean algebraic difference for the 28 values is calculated.
2. Mean of Absolute Differences: The absolute side-to-side difference beween each of the 28 Z_{same} impedance values is taken, and the mean absolute difference for the 28 values is calculated.
3. Number of Matches: The number of mirror image matching impedance chords, referred to in the discussion of FIG.10. A related statistic, the Number of Mismatches = 28 - Number of Matches.
4. Mean of Algebraic Differences/ Number of Mismatches.
5. Mean of Absolute Differences/ Number of Mismatches

Confidence intervals about these means are calculated based on measures such as one or two standard deviations. Some or all of these statistics, and/or other ones derived from the impedance matrix, eigenvalues or eigenvectors, are used as part of a diagnostic algorithm for breast cancer screening, as shown in FIG. 11. The mean side-to-side difference statistics generated by the impedance scan are examined (preferentially by computer) to determine whether a significant number of the means or certain subsets of means, weighted or otherwise, fall within the confidence limits of normal or cancer groups. If the determination is for the normal group, the impedance scan is normal; if the determination is for the cancer group, a breast cancer is suspected, and the match-removed chord plot of normalized Z_{same} impedances is obtained to indicate tumor location, followed by other procedures such as X-ray mammography.

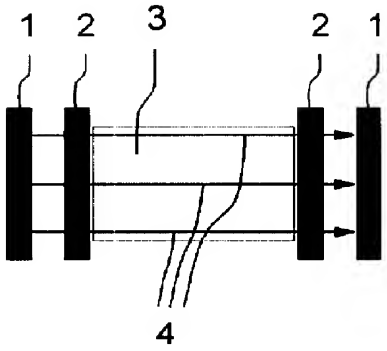


FIG. 1

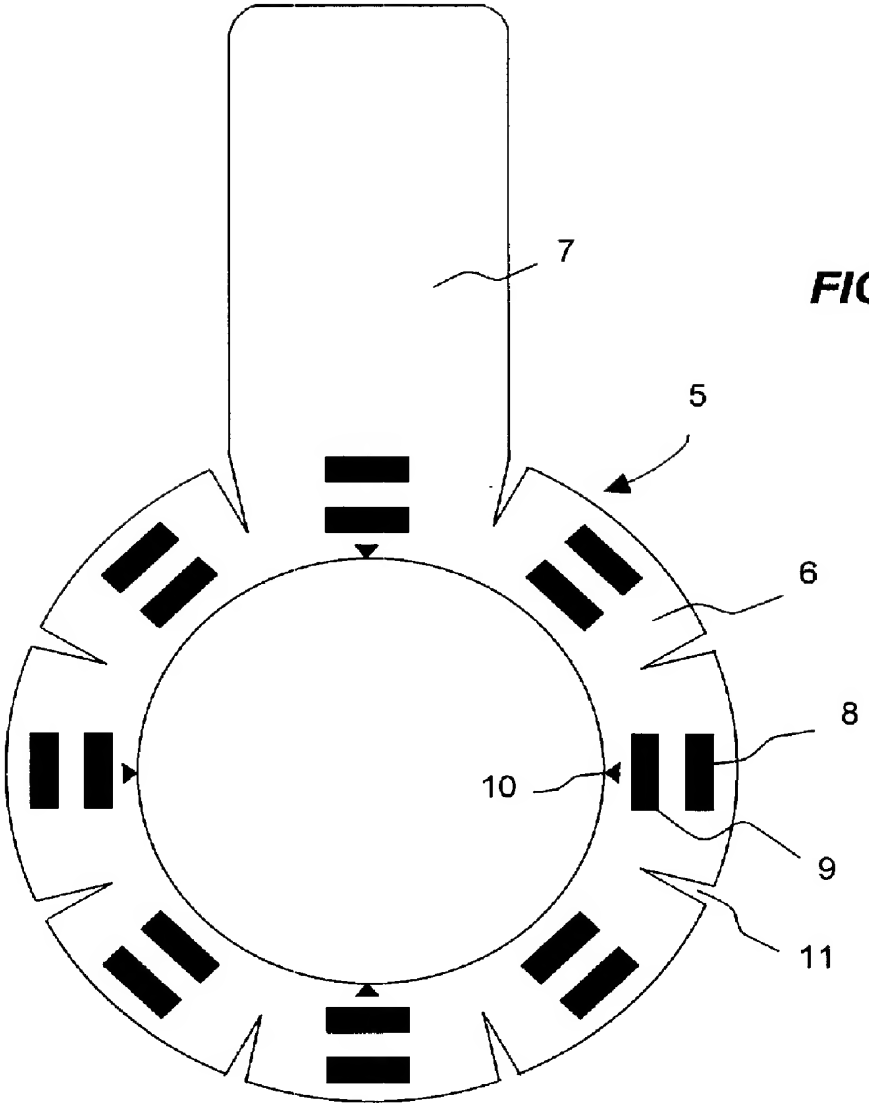


FIG. 2

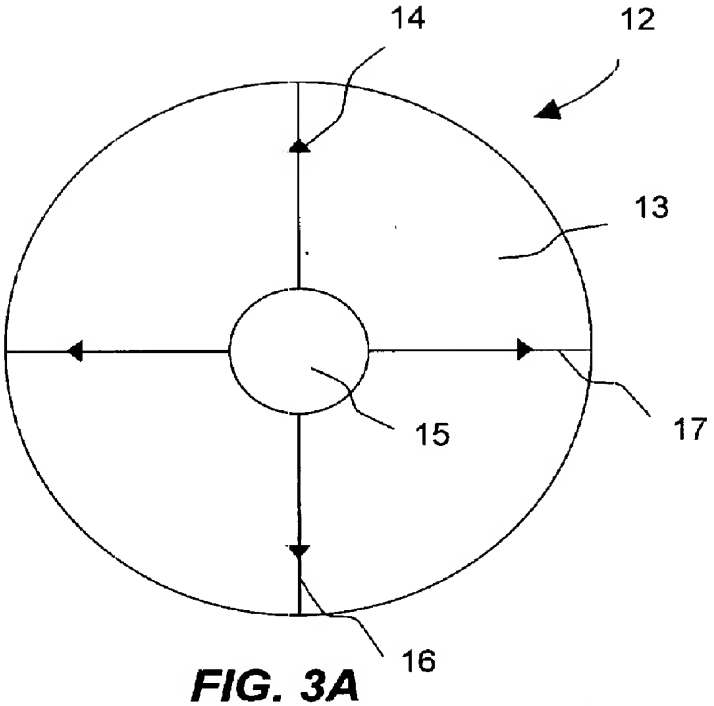


FIG. 3A

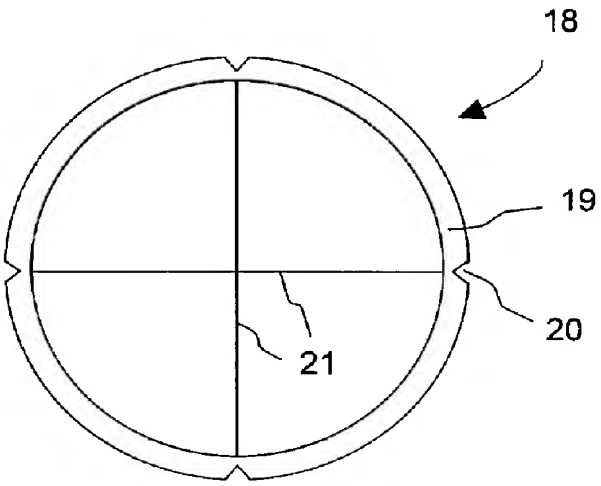


FIG. 3B

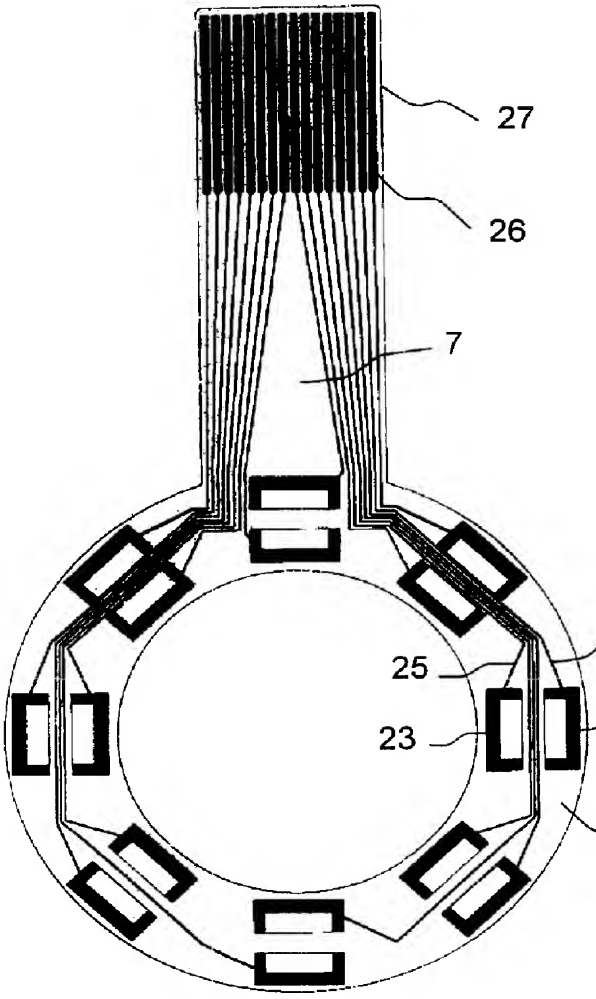


FIG. 4

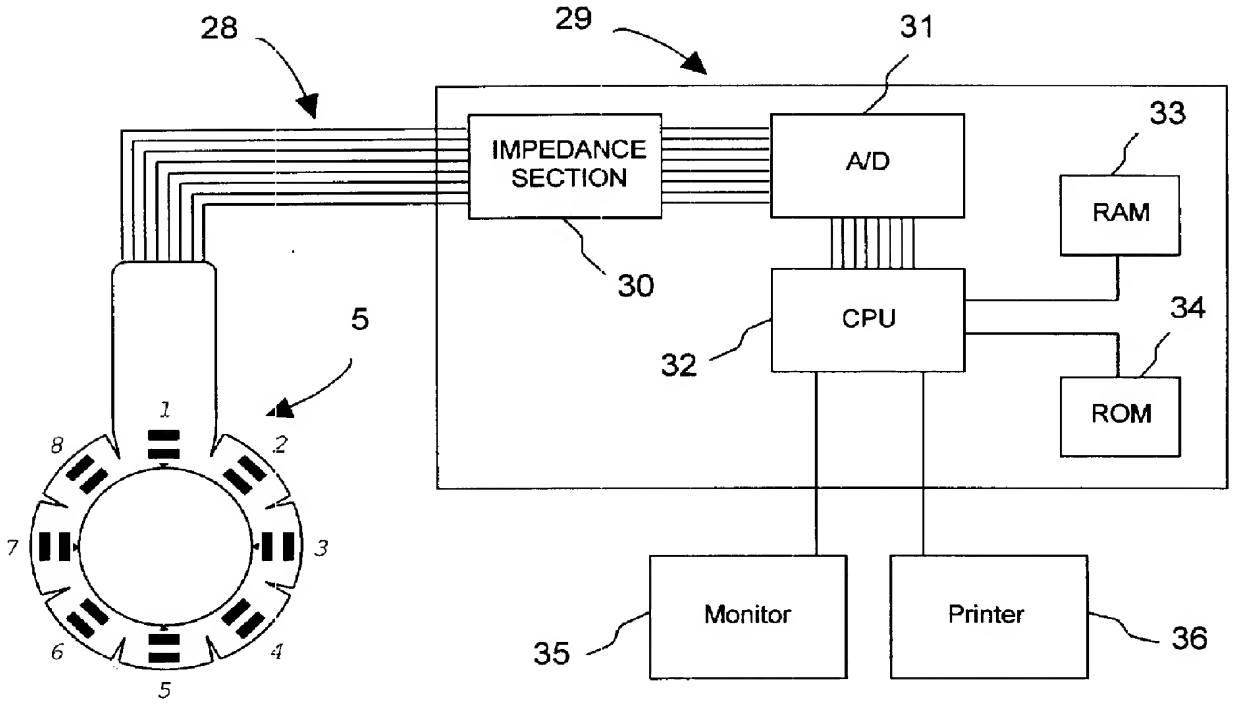

28
29
31
33
IMPEDANCE SECTION
A/D
RAM
30
5
CPU
34
32
ROM
1
2
3
4
5
6
7
8
Monitor
Printer
35
36

FIG. 5

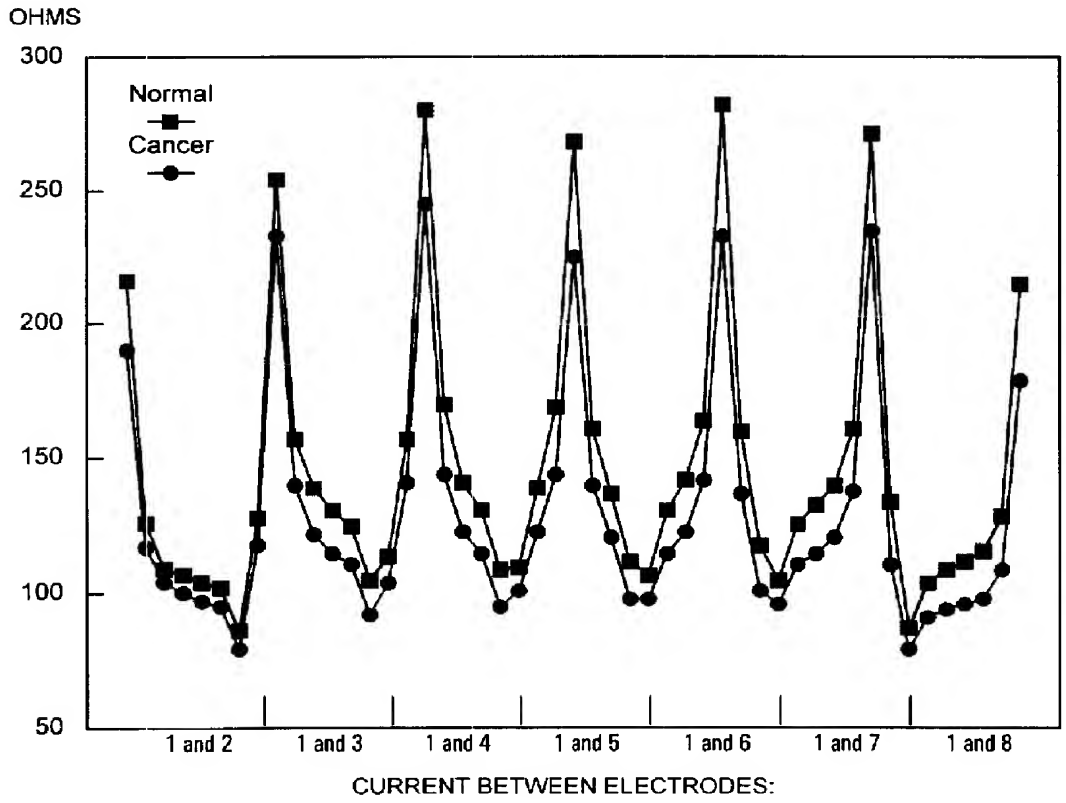

OHMS
300
250
200
150
100
50
Normal
Cancer
1 and 2
1 and 3
1 and 4
1 and 5
1 and 6
1 and 7
1 and 8
CURRENT BETWEEN ELECTRODES:

FIG. 6

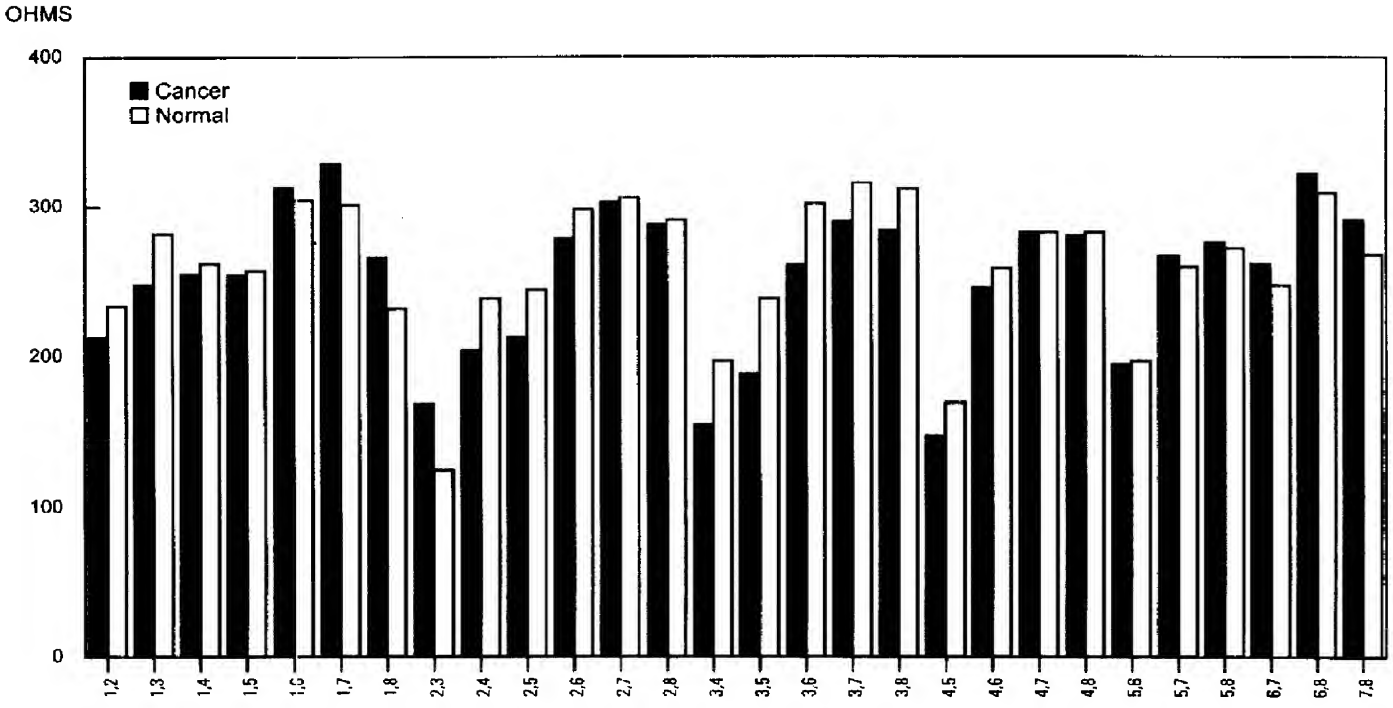

OHMS
400
300
200
100
0
Cancer
Normal
1,2
1,3
1,4
1,5
1,6
1,7
1,8
2,3
2,4
2,5
2,6
2,7
2,8
3,4
3,5
3,6
3,7
3,8
4,5
4,6
4,7
4,8
5,6
5,7
5,8
6,7
6,8
7,8

FIG. 7

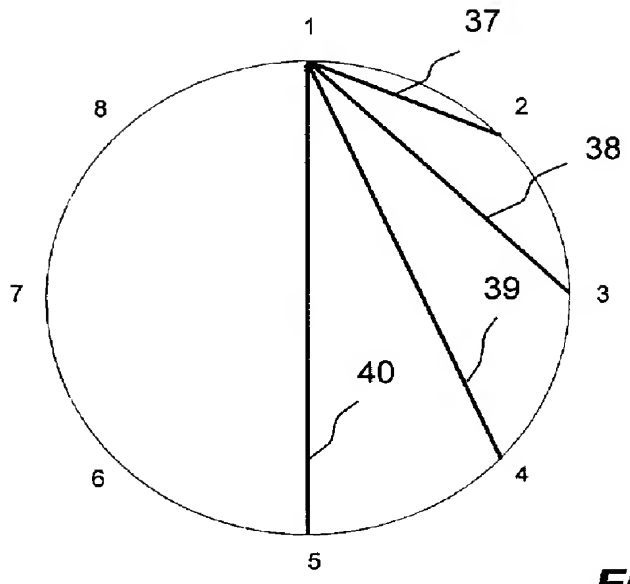

1
2
3
4
5
6
7
8
37
38
39
40

FIG. 8

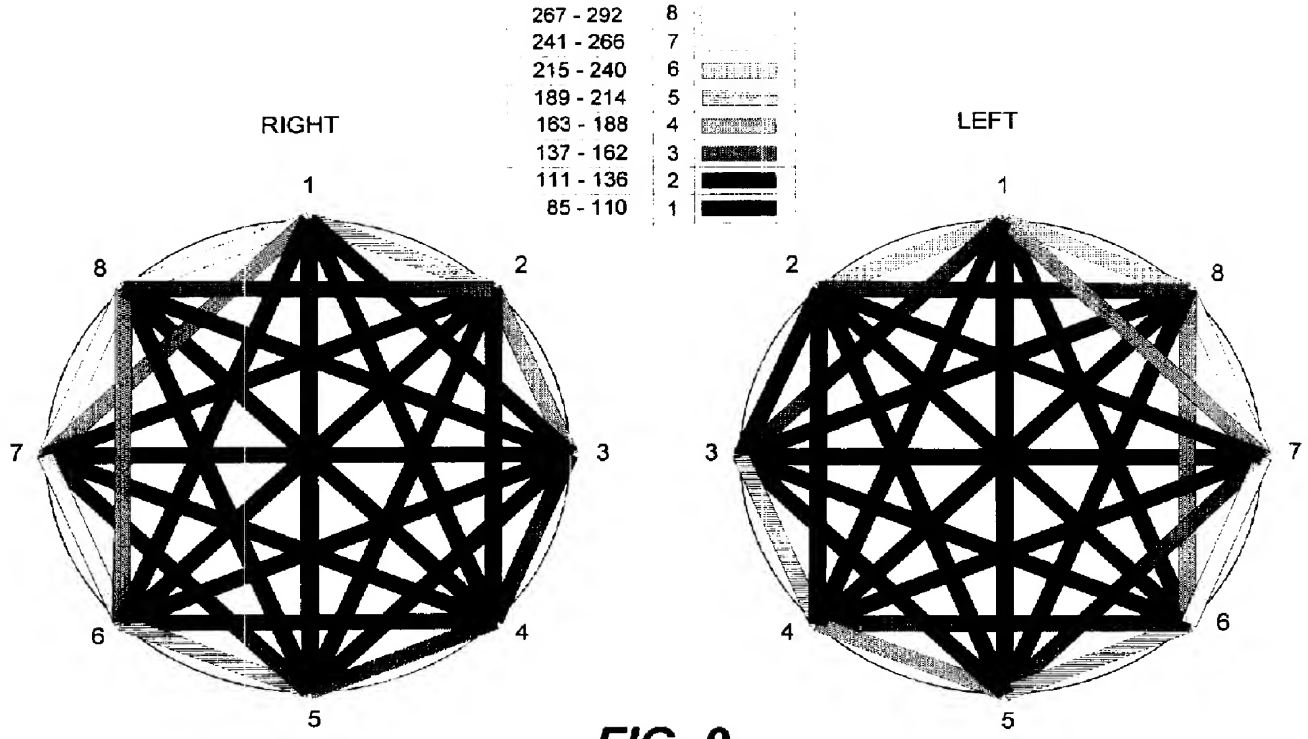
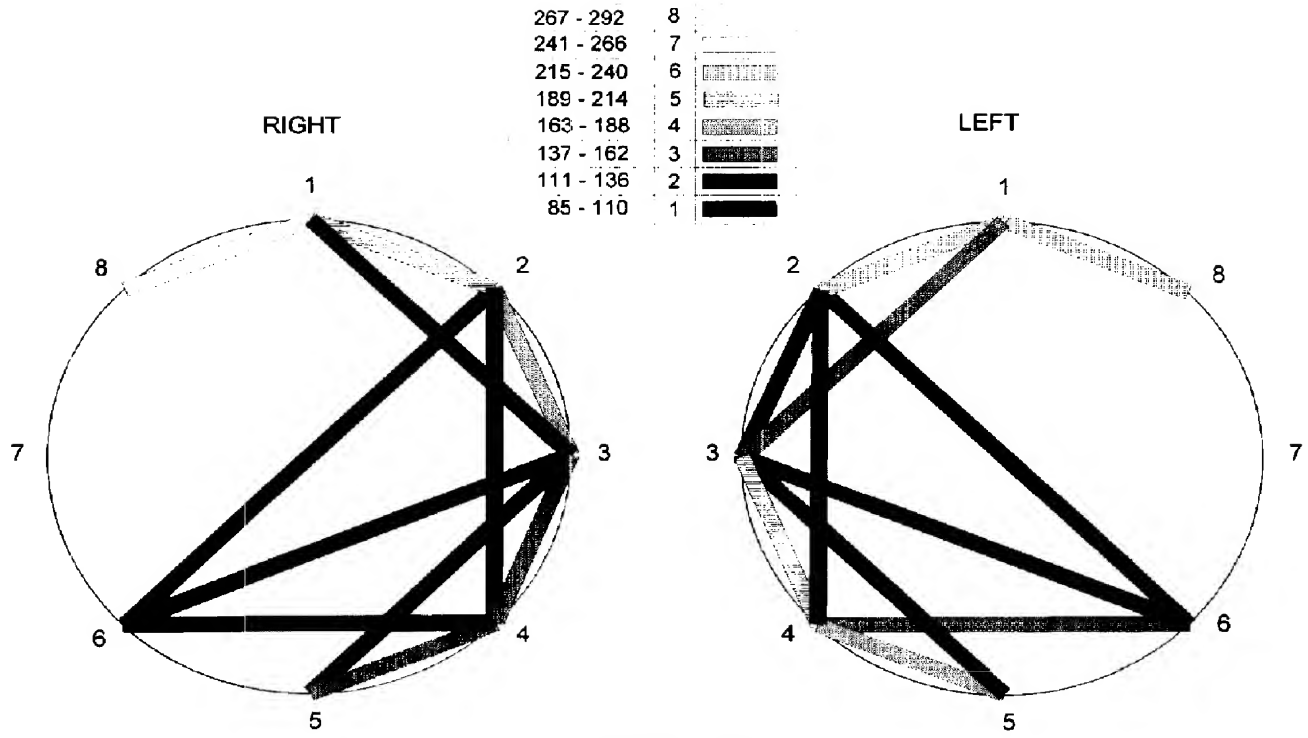

267 - 292 8
241 - 266 7
215 - 240 6
189 - 214 5
163 - 188 4
137 - 162 3
111 - 136 2
85 - 110 1
RIGHT
LEFT
1
2
3
4
5
6
7
8

FIG. 9


267 - 292 8
241 - 266 7
215 - 240 6
189 - 214 5
163 - 188 4
137 - 162 3
111 - 136 2
85 - 110 1
RIGHT
LEFT
1
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3
4
5
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7
8

FIG. 10

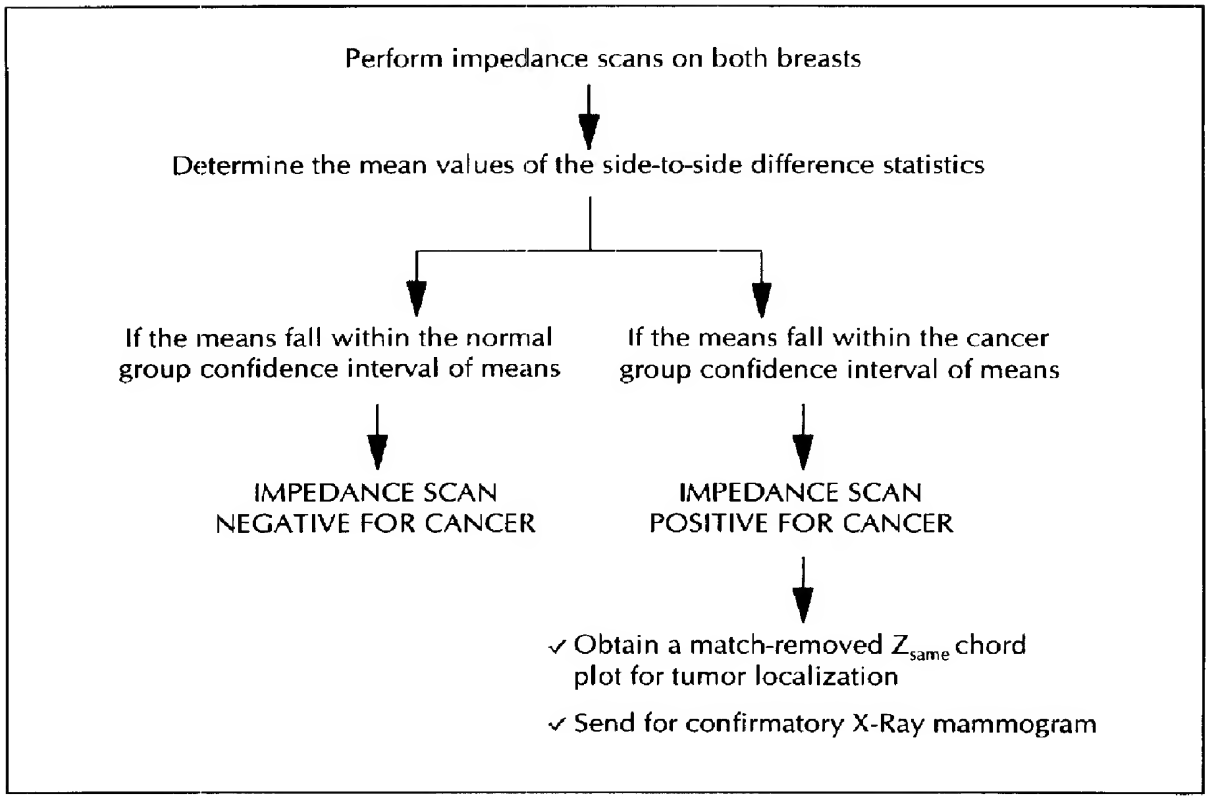
Perform impedance scans on both breasts
Determine the mean values of the side-to-side difference statistics
If the means fall within the normal group confidence interval of means
If the means fall within the cancer group confidence interval of means
IMPEDANCE SCAN NEGATIVE FOR CANCER
IMPEDANCE SCAN POSITIVE FOR CANCER
✓ Obtain a match-removed Z_{same} chord plot for tumor localization
✓ Send for confirmatory X-Ray mammogram

FIG. 11